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Original article

Household storage of pharmaceutical products in Saudi Arabia; A call for utilising smart packaging solutions

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ABSTRACT

Background: Limited information is known about the storage conditions of medicinal products post-dispensing in Saudi Arabia (SA). The particularly hot and humid climate in the region may lead to the loss of essential performance specifications.
Objective: To investigate the conditions in which medications are held after being dispensed, and up until administration by households in SA. In addition, storage practices adopted by households in the region, as well as their knowledge and awareness are explored. This study also discusses the opportunity of utilising Time-Temperature Indicators (TTIs) in the pharmaceutical industry in SA as a quality-assurance enhancement solution.
Methods: A cross-sectional questionnaire targeted at households in SA was designed to explore storage practices, background knowledge and awareness of factors that can influence drug stability. Additionally, temperature and relative humidity mapping of 35 different rooms in various homes and cities in SA, as well as car interiors, was performed.
Results: More than 1000 households have participated in this study from all regions of SA. Approximately, 95% have claimed to take part in storing medications at home. First-aid and supplemental purposes were two of the reasons 80.9% have claimed, while 43.2% claimed treatment for chronic conditions. Just over 35% claimed that not knowing how to dispose of medications, is the reason behind their storage. More than 35% of participants could not identify most suitable storage conditions, and >10% were unaware of the effect storage conditions may have on shelf-life. Many were found to store medication in inappropriate areas, liquid dosage forms for example were stored in freezers by more than 3%. Upon monitoring temperatures of all room types, 25ºC was exceeded throughout a 24-hour duration in bathrooms, kitchens and limited use rooms. Temperatures in parked car interiors exceeded 70ºC.
Conclusions: A significant percentage of households in SA lacked knowledge and awareness of good storage practices. However, due to high temperatures observed in the region, increasing knowledge and awareness is not enough, as medicinal cabinets with basic temperature control (e.g. designated secure fridge) are needed. Additionally, the use of TTIs to provide consumers with accumulated thermal history may enhance quality-assurance of thermally sensitive products.

1. Introduction

The performance of pharmaceutical products can be greatly influenced by the stability of its components, specifically the Active Pharmaceutical Ingredient (API) (Alqurshi et al., 2016; Altebainawi et al., 2020). Exposure to storage conditions outside the manufacturer's recommended range can shorten pharmaceutical product shelf-life and may even lead to the creation of harmful degradation products (Waterman, 2011; Malallah et al., 2020). Factors that can influence storage conditions include temperature, humidity, light and in some cases direct contact with oxygen or other air components (ICH, 1996a,b, 2002, 2003a,b). In addition to the degradation of APIs, harmful storage conditions can strip pharmaceutical products of their physicochemical properties essential for their performance in safely carrying and delivering medicine (Craig et al., 1999; Alqurshi et al., 2017; Malallah et al., 2020). Depending on the climate of the region in which products are intended for marketing, the International Conference on Harmonisation, of

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Table 1
Storage conditions specified by ICH and WHO guidelines for stability testing. Different parts of the world were assigned one of five climatic zones depending on prevailing annual climatic conditions (ICH, 2003). According to the WHO, Saudi Arabia falls under climatic zone IV_a where long-term stability testing conditions are 30 ± 2 °C/65 ± 5% RH (WHO, 2015).

Study type	Climatic Zone I & II		Climatic Zone III, IV_a & IV_b	
	Temp/°C	RH%	Temp/°C	RH%
Long-term (>12 months)	30 ± 2[a]	65 ± 5% [a]	25–30 ± 2[b]	60–75 ± 5%[b]
Accelerated (>6 months)	40 ± 2	75 ± 5%	40 ± 2	75 ± 5%

[a] A choice of 25 °C ± 2 °C/60% ±5% is available as an alternative for applicants.
[b] Depending on the climatic zone assigned by the WHO, storage conditions can be either 25 ± 2 °C/60 ± 5% RH or 30 ± 2 °C/65 ± 5% RH or 30 ± 2 °C/75 ± 5% RH (WHO 2009).

technical requirements for registration of pharmaceuticals for human use, (ICH) and the World Health Organisation (WHO) has specified various storage conditions (Table 1) for stability testing (ICH, 1996a,b, 2002, 2003a,b). This is also adopted by the Gulf Cooperation Council (GCC, 2001), and therefore regulatory bodies in the region such as the Saudi Food and Drug Authority (SFDA). Derived from a long-term stability study, manufactures specify expiration dates based on defined storage conditions that can maintain essential specifications intact for the duration of the shelf-life (ICH, 2003a,b). Complying with manufacturers' storage instructions, such as recommended storage temperature and humidity, is considered the definition of good in-home storage practice. Alternatively, inappropriate in-home storage practices may include overlooking manufacturers' instructions, such as exposing pharmaceutical products to high temperatures and/or humidity, which as a result may lead to their spoilage.

A recent study by Altebainawi et al. (2020) has alerted readers in the Saudi Arabian pharmaceutical society to the effect of storage conditions on diabetes medication and effectively managing blood glucose levels. Similarly, storage conditions may also limit the effectiveness of other medications commonly stored by households in Saudi Arabia. Due to the high temperatures observed in the country (Howarth et al., 2020), maintaining pharmaceutical products within ranges specified by manufacturers may be more challenging than in other climates. Although most residential buildings are equipped with air conditioning and thermal isolation, indoor temperatures may exceed the U.S. Pharmacopeia's definition of room temperature (20–25 °C) depending on occupancy and air conditioning (Cohen et al., 2007).

Koshok et al. (2017) published that the majority of consumers claim to avoid using medications when a change of colour is observed. However, unlike food, spoilage of medication when exposed to undesirable conditions is not easily detectable by consumers. The food industry has tackled such issues with extensive research in smart packaging solutions, including Time-Temperature Indicators (TTIs) (Wang et al., 2015; Yousefi et al., 2019). TTIs may be described as small devices, that can come in the form of labels, to provide consumers with a clear signal of accumulated thermal history (Wang et al., 2015). Such technologies are based on irreversible change in colour, or other clear indication, induced by the accumulated effects of storage outside specified temperature range (Wang et al., 2015). The numerus studies and patents reviewed by Wang et al. (2015) and Choi et al. (2020) in this field can potentially provide a rich platform for designing various TTIs suitable for storage temperatures specified by pharmaceutical manufacturers. Furthering the implementation of such technologies in the pharmaceutical industry would not only protect consumers from administering harmful degradation products, but also provide useful information on the remaining shelf-life if such products were exposed to harmful storage conditions (Taoukis and Labuza, 1989; Gao et al., 2020).

The aim of this study is to investigate the conditions in which medications are held after being dispensed, and up until administration, by patients in Saudi Arabia. This includes temperatures and relative humidity (%RH) of private transportation and home storage. In addition, storage practices adopted by households in the region are explored. This study also discusses the opportunity of utilising TTIs in the pharmaceutical industry in Saudi Arabia as a quality-assurance enhancement solution.

2. Methods

2.1. Cross-sectional questionnaire.

An anonymous online form-based questionnaire was designed to investigate household awareness and practices towards storage of medicines at home. The questionnaire began with a demographic section followed by determining if participants stored medications at home and why, in addition to identifying categories of medicines stored. This was followed by assessment of household compliance with good storage practices, as well as their awareness and background knowledge on factors that influence stability and shelf-life of pharmaceutical products. Questions followed the formats of a multiple choice, 5-point Likert-scale and rubric based choices to simplify the participation process. Additionally, in alignment with recent research on the factors influencing response rate to digital questionnaires, a progress bar was made visible for participants to feel more invested while moving through the questionnaire (Tukibayeva and Sarraf, 2012). Finally, participant satisfaction with effectiveness of home stored medication was assessed, based on a 5-point scoring scale, to further investigate the perceived efficacy by patients with varying storage practices.

With the aim of limiting response bias, the questionnaire was optimised via a series of piolet tests, performed by several volunteers including linguistics and psychology experts. After each optimisation cycle, the pilot group were invited to provide their feedback in an online session. In the process of optimisation, the language used in the questionnaire was simplified to allow participants with no medical background fully understand stated questions. Additionally, an option of skipping non-essential questions was made available, while Likert-scale questions contained 5 choices, giving participants a neutral response (Croasmun and Ostrom, 2011). Furthermore, a choice of typing in an alternative answer was also provided to give participants more freedom in their response (Furnham, 1986; Bogner and Landrock, 2016).

2.1.1. Determining appropriate sample size

The questionnaire was designed to collect continuous and categorical data. However, for the purpose of determining the largest appropriate sample size, the categorical data generated from questions relating to storage conditions were assigned as the primary variable for measurement (Kotrlik and Higgins, 2001). Target sample size was therefore determined using the Cochran's formula (Kotrlik and Higgins, 2001) for categorical data (presented below).

$$n = \frac{t^2 \cdot p \cdot (1-p)}{d^2}$$

"*n*" is the appropriate sample size to be calculated. "*t*" is the t-value corresponding to the percentage level of confidence for a determined population size (The invert of such percentage is referred to as the Alpha level or the level of acceptable risk). Adapted from previous studies, a 95% level of confidence was set for this study (Kotrlik and Higgins, 2001; Taherdoost, 2017). Assuming population size >120, the corresponding t-value for a 95% level of confidence equals a value of 1.96 (Kotrlik and Higgins, 2001). "*d*" is the acceptable margin of error, set to be between 5 and 3% to represent both categorical and continuous data (Kotrlik and Higgins, 2001). A recommended value for the population proportion "*p*", when undetermined, is 0.5 (Kotrlik and Higgins, 2001). Thus, ensuring the largest possible estimated variance in the primary variable and therefore sample size (Kotrlik and Higgins, 2001; Taherdoost, 2017). Building on the abovementioned parameters, the minimal sample size for this study was determined to be between 385 and 1068 participants for a 5–3% acceptable margin of error, respectively.

2.1.2. Data collection

Using digital platforms such as "*twitter*" and "*WhatsApp*", the questionnaire was distributed among households in all 13 regions of Saudi Arabia. Assuming a low response rate, as observed in previous studies (Koshok et al., 2017), a proactive campaign of retweeting and distributing the questionnaire was adopted through twitter accounts with large numbers of followers.

Table 2
Demographic details of collected sample (**n = 1005**). To avoid biased assessment, participants with medical background (including students in medical courses such as pharmacy and medicine as well as participants employed in a medically influenced environment) were separately analysed. Collected sample contains 752 participants with non-medical background and 253 participants with medical background. 4.7% of participants claimed to never store medication at home, and 13.1% claimed to occasionally store medicines, while 82.2% claimed to always store medicines at home. Questionnaires distributed via "*twitter*" delivered a response rate of 5.5% (according to twitter analytics tool). Acquiring number of distributed questionnaires via WhatsApp was not possible, thus no response rate was determined. Participants who have not consented to the use of their data have been excluded.

Variables	No. of participants (%)	
	Non-medical	Medical
Gender		
Male	421 (41.89)	171 (17.01)
Female	331 (32.94)	82 (8.16)
Age group		
$X \leq 20$	31 (3.08)	31 (3.08)
$20 < X \leq 30$	163 (16.22)	115 11.44)
$30 < X \leq 40$	221 (21.99)	69 (6.8)
$40 < X \leq 50$	187 (18.61)	17 (1.69)
$50 < X \leq 60$	112 (11.14)	15 (1.49)
$60 < X$	38 (3.78)	6 (0.60)
Education qualification		
None	10 (1.00)	–
High school qualification	125 (12.44)	5 (0.50)*
Diploma	66 (6.57)	29 (2.89)
Currently studying bachelor degree	36 (3.58)	57 (5.67)
Bachelor qualification	400 (39.80)	112 (11.14)
Masters qualification	75 (7.46)	25 (2.49)
PhD qualification	40 (3.98)	25 (2.49)
Region		
Asir	7 (0.70)	6 (0.60)
Bahah	2 (0.20)	4 (0.40)
Eastern Province	45 (4.48)	16 (1.59)
Hail	8 (0.80)	–
Jouf	2 (0.20)	–
Jizan	7 (0.70)	1 (0.10)
Madinah	173 (17.21)	112 (11.14)
Makkah	291 (28.96)	61 (6.07)
Najran	–	1 (0.10)
Northern Borders	2 (0.20)	–
Qassim	26 (2.59)	13 (1.29)
Riyadh	180 (17.91)	35 (3.48)
Tabuk	9 (0.90)	4 (0.40)

* This may include students at diploma level in medical based courses and/or employed in a medically influenced environments such as pharmaceutical manufacturing companies.

2.1.3. Data analysis

Data collected from various types of questions including ones based on Likert-scales were analysed using various software (Microsoft Excel and Origin 2018b). Processed data was presented using appropriate charts (e.g. divergent bar charts for Likert-scale based questions). Statistical tests including one and two-way ANOVA were performed using IBM® SPSS statistics software.

2.2. Temperature and % relative humidity mapping

Using a calibrated data logger (BST-DL14, purchased from BESANTEK), the temperature and relative humidity (%RH) of five types of rooms were monitored over a period of 24-hours. The data logger was positioned in drawers (if available) and not in direct exposure to sun light, a source of artificial heat or air conditioning. Room types included: Bedrooms, Bathrooms, Kitchens, Living rooms and limited use rooms. The experiment was repeated in different rooms of the same type ($n \geq 6$). The process included the participation of 7 households across 3 cities (Jeddah, Medina and Khobar) in Saudi Arabia. Temperature and %RH were also monitored over a 24-hour period in a parked car (directly exposed to sunlight). The experiment was performed in Jeddah and Medina.

Experimental settings were designed to simulate storage of medicinal products in different areas. Recording intervals for temperature and %RH were 60 s. Prior to recording measurements, data loggers were allowed a minimum of 30 min to ensure equilibration with room temperature. Recorded temperatures and %RH were analysed using data logger software (BSTSoftware, provided by BESANTEK). Calculation of Mean Kinetic Temperature (MKT) was performed for each (24-hour period) experiment to express the constant temperature impacting stored medicinal products (Kim et al., 2020)

3. Results

The E-based questionnaire yielded just over 1000 responses from all thirteen regions of the Kingdom and all age groups (Table 2 demonstrates key demographic data). Assuming a 95% confidence level, and 0.5 population proportion, the margin of error for the sample size was determined, using Cochran's formula (Kotrlik and Higgins, 2001) for categorical data, to equal 3.1%. While participants varied in level of education, approximately 30% claimed to have a medical background, leaving approximately 70% of participants with no medical background (Table 2).

Storing medications at home was defined for the purpose of this study as keeping a medicinal or pharmaceutical product at home for more than 30 days. While 4.7% of participants claimed to never store medications at home, approximately 13.1% claimed to sometimes do. Leaving 82.2% of participants claiming to always have medicines stored at home. The purpose of storage, most participants have claimed (80.9%) is first aid and supplemental. Treatment for chronic conditions was also another reason claimed by 43.2% of participants. Furthermore, 36.7% of participants have claimed to store leftover medications from either an acute condition or a previously halted course of medications for a chronic condition, not knowing how to dispose of them.

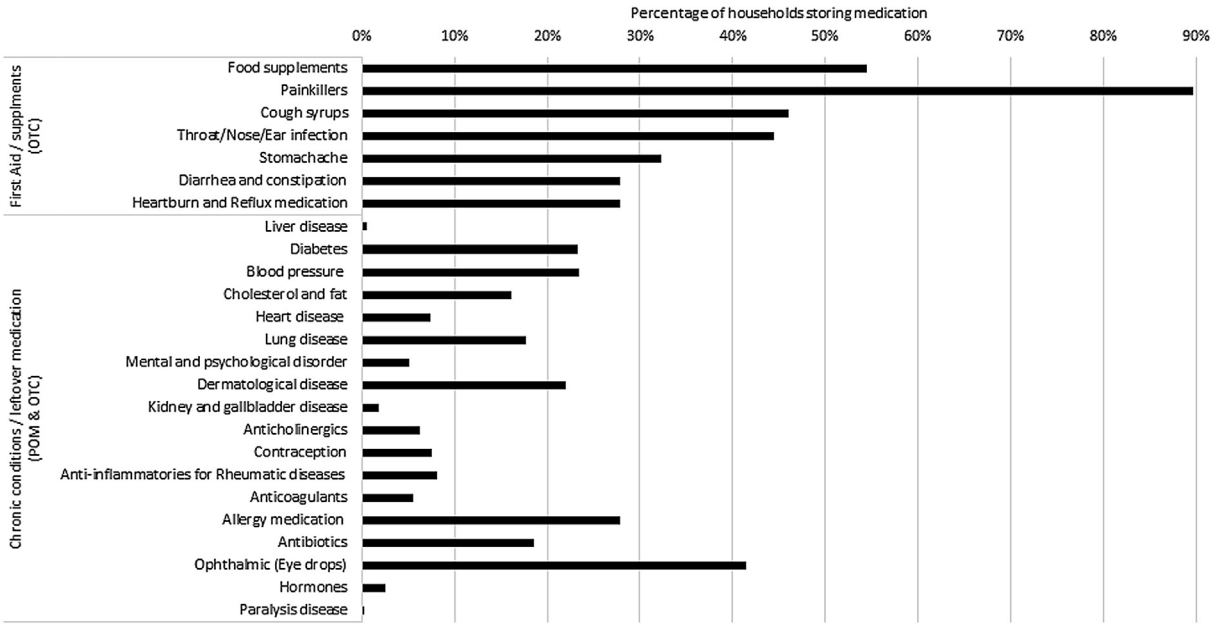

Fig. 1. Percentages of households in Saudi Arabia claiming to store medicines at home, categorised by medication type **(n = 959)**. Participants could select more than one category of medication. Common terminologies where used to help non-medical participants identify the type of medication stored at home. Storage period in this study is defined as a period >30 days. In preliminary parts of the questionnaire, just over 80% of households claimed one of their reasons for storing medications is first aid and supplemental purposes, while 43% claimed to store medications for chronic illness treatments and just under 37% claimed to store residual medications (from acute conditions or changes in treatment of chronic conditions) due to not knowing how to properly dispose of them.

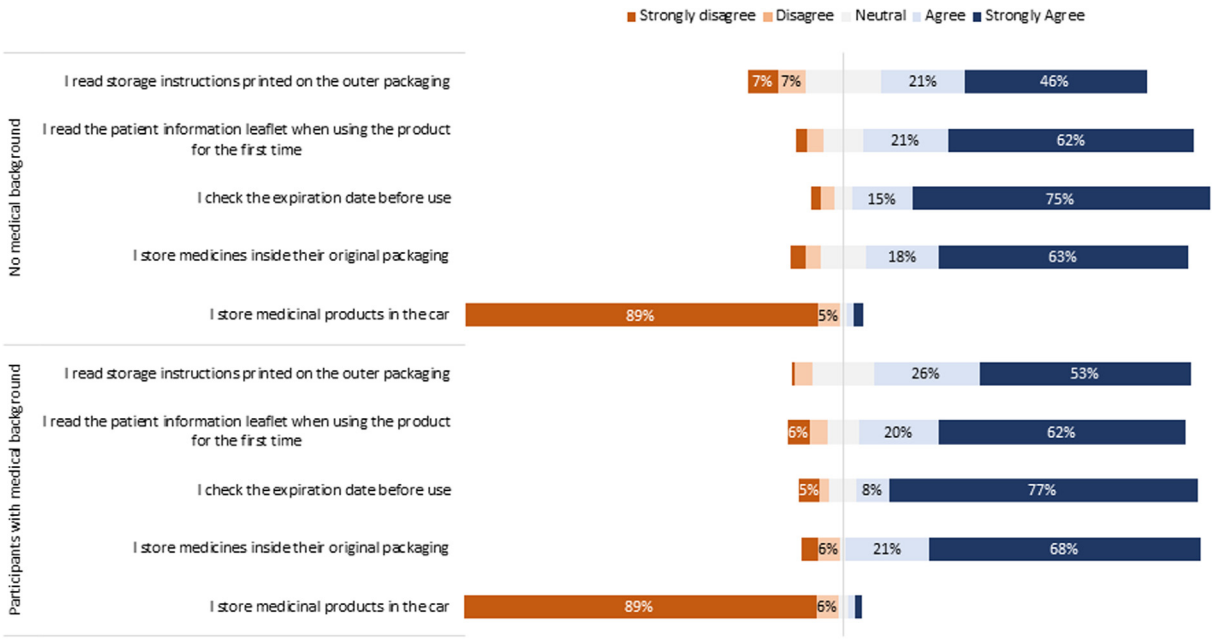

Fig. 2. Divergent stacked bar chart presenting participants level of agreement with phrases relating to medicinal storage practices as part of 5-point Likert-scale questions. Responses from participants with no medical background are presented at the top part of the figure (n = 752), followed by participants with medical background (n = 253). Bars with values lower than 5% contain no data label.

3.1. Commonly stored medications

In further investigating types of medications stored by participants, approximately nine out of ten households were found to store Over-The-Counter (OTC) painkillers (Fig. 1). These may include the most popular OTC Analgesics such as Paracetamol (Lefterova and Getov, 2004; Al-Shalabi et al., 2012). Manufacturers of pharmaceutical products containing such APIs usually instruct storage below 25 °C (Al-Shalabi et al., 2012). Food supplements, including multivitamins are being stored by more than 50% of participants in this study (Fig. 1). Cough syrups and medications for throat, nose and ear infections are both stored by more than 40% of participants (Fig. 1). Medication for stomach-ache, diarrhoea, constipation, heartburn and acid reflux are all approximately stored by 27% of participants (Fig. 1).

Stored medications for purposes of treating chronic conditions are categorised by condition in Fig. 1. Apart from eyedrops and allergy related pharmaceutical products (which may be cate-

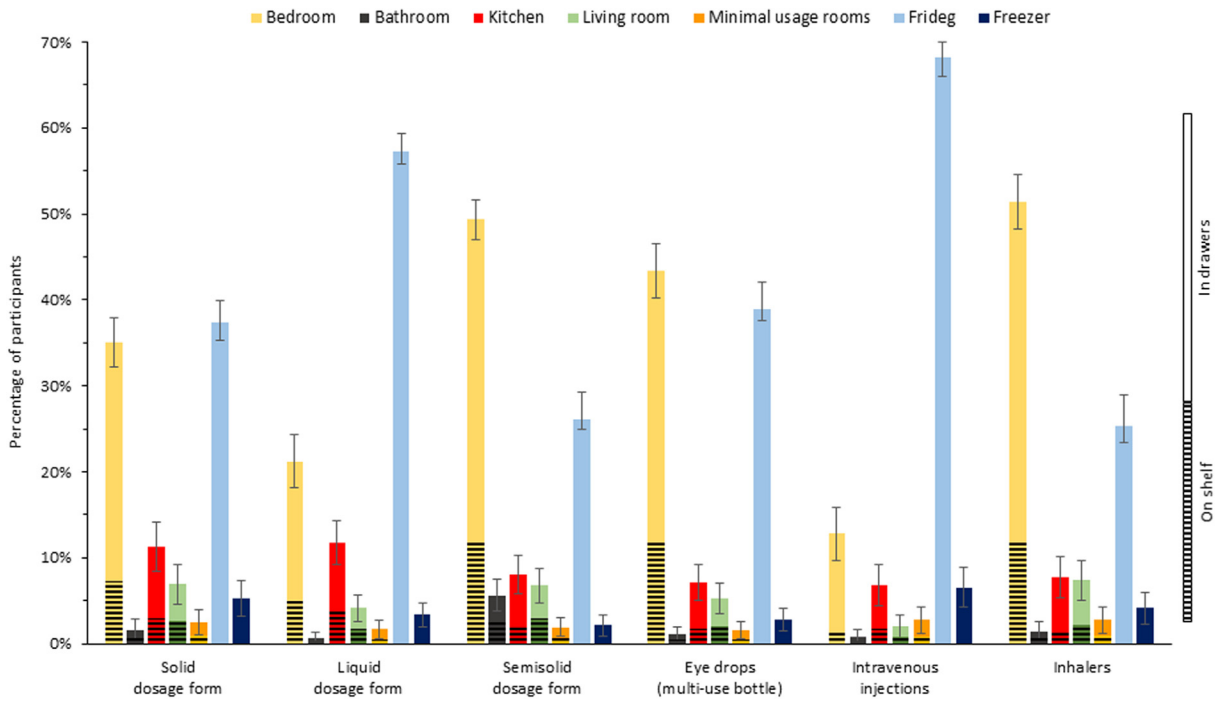

Fig. 3. Storage details of medications by households in Saudi Arabia categorised by pharmaceutical dosage form. Participants were asked to only responded for dosage forms they are used to storing at home, thus number of participants for each dosage form differs: Solid dosage form **(n = 892)**, Liquid dosage form **(n = 909)**, Semisolid dosage form **(n = 937)**, Eye drops **(n = 875)**, Intravenous injections **(n = 599)**, Inhalers **(n = 670)**. Storage information included room type and "on shelf" or "in drawer" positions, presented by stripe or solid colour, respectively. Error bars represent margin of error based on sample proportion and a confidence level of 95%. All products stored in fridge or freezer were considered in drawer.

gorised as OTC), Prescription Only Medications (POMs) for diabetes and blood pressure were found to be the most commonly stored for chronic condition treatments (Fig. 1).

3.2. Storage practices and awareness

In response to a series of 5-point Likert-scale questions on medicinal storage practices, the majority (≥65%) of households, including participants with no medical background, claimed to follow good storage practices (Fig. 2). These included reading printed storage instructions and patient information leaflets, checking the expiration date before use, and finally storing dosage forms in their original packaging. Nevertheless, there remains a significant percentage of households (5–14%) admitting not to perform the above-mentioned good storage practices (Fig. 2).

More than 90% of all households have strongly disagreed with the practice of storing medicines in a car (Fig. 2), and approximately 30% of participants from both groups (with and without medical background) claimed to own a designated medicine cabinet.

To evaluate participant knowledge and awareness of good storage practices of medicinal products, participants were asked to take part in a short test. This involved identifying storage factors that can influence stability of medicinal products; 96% of participants selected "Storage temperature" as one of the factors, "Exposure to light" was selected by 53%, "Humidity" was selected by 77% and "Direct exposure to air content" was selected only by 25%. Furthermore, when participants were asked to choose the most suitable storage conditions from a provided list of conditions, the majority (63%) selected "Dry and dark storage areas", 8.9% selected "Dry and exposed to light storage areas", 6.5% selected "Humid and dark storage areas", 3.2% selected "Humid and exposed to light storage areas" and finally 18.4% opted to not knowing the most appropriate storage conditions. In a final question, approximately 87% of participants agreed that storing medicinal products outside the manufacturer's specified storage conditions can lead to reducing their shelf-life, 1% of participants disagreed and the remaining 13% were not sure.

Participants with no medical background have scored an average of 3.2 ± 1.2 out of 5 points while those with a medical background have scored an average of 4.1 ± 0.8. Using unpaired two-tailed unequal variance *t*-test (Kim, 2015), the performance of participants with medical background was determined significantly higher than those with no medical background ($p < 0.05$).

In investigating commonly used areas for storing medicinal products, households were provided with a rubric of "room type" and "position of storage" (i.e. in drawer or on shelf) to allow prediction of storage conditions. In addition, a choice of storage in fridge or freezer was available as part of the rubric. Fig. 3 summarises common storage areas claimed by participants for six pharmaceutical dosage forms. Number of participants for each dosage form varies according to its storage popularity.

Results show most used areas for storing medicinal products are bedrooms (in drawers) and fridges (Fig. 3). Nevertheless, a substantial percentage of participants (17–26%) claimed to commonly store medicinal products in other areas of the house, including kitchen drawers, living room drawers, bathrooms, limited use rooms and freezers (Fig. 3). Approximately 3% of participants have claimed to commonly store liquid dosage forms in a freezer (Fig. 3). Using a 2-way ANOVA analysis, patients admitting to store medications in bathrooms were found to rate the performance of their medications significantly lower than all other groups ($p < 0.05$).

3.3. Temperature and % RH mapping of different storage areas

3.3.1. Validation of temperature and % RH measurements

Purchased data loggers (for logging temperature and % RH measurements) were provided with a calibration certificate. Neverthe-

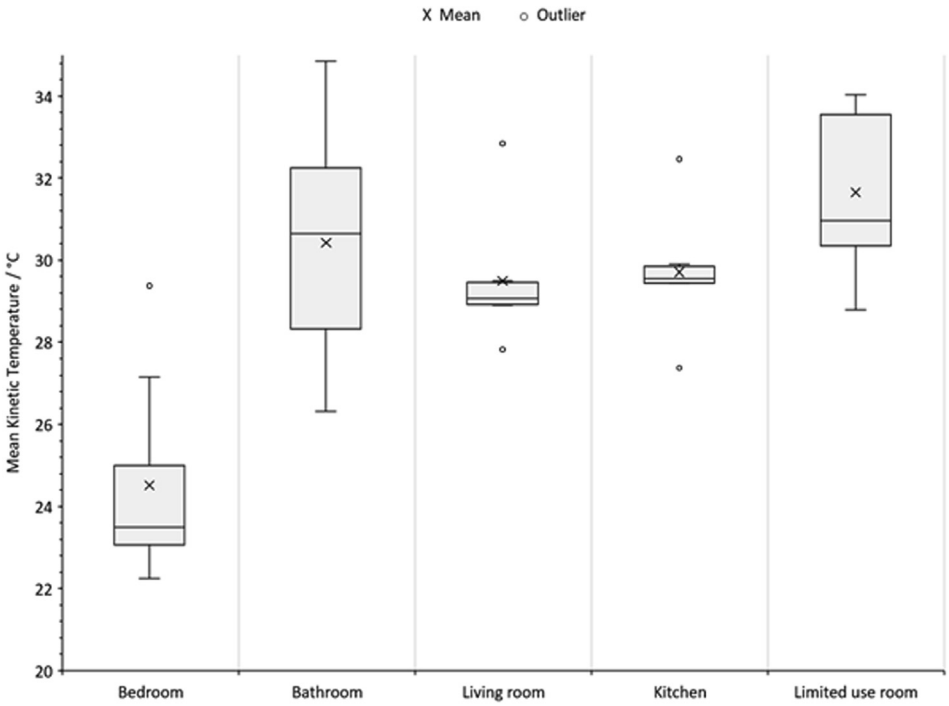

Fig. 4. Box Plot (McGill et al., 1978) to demonstrate and compare the Mean Kinetic Temperature (MKT) of various in house storage areas over a 24 h period, grouped by room type. Measurements were completed in June and July (year 2020) using a calibrated temperature and %RH logger (±0.5 °C, ±5%RH at 25 °C). For each room type, the 1st and 3rd quartiles of MKT values are represented by the upper and lower horizontal borders respectively (McGill et al., 1978, Wickham and Stryjewski 2011). Highest and lowest MKT values for each group are represented by the upper and lower whiskers respectively (McGill et al., 1978, Wickham and Stryjewski 2011). Horizontal line inside each box marks the median. The MKT values for the kitchen group are densely populated between 29 and 30 °C, thus causing the bottom whisker to overlap with the 3rd quartile. Using the interquartile range (IQR) rule (Schwertman et al., 2004) outliers were determined and presented. Measurements where performed in 7 different houses located in Jeddah, Medina and Khobar. For each room type the observed range of temperature and %RH is presented in table 3.

Table 3
Ranges of room temperature and %RH values categorised by storage area (Room type/Car) and city. Values on the lowest row represent pooled averages of mean kinetic temperatures (MKT) for rooms of the same type, and %RH, ±standard deviation of n ≥ 6 for room type based measurements and n = 2 for car-based measurements. Pooled average and standard deviation values were calculated by pooling together the averages of MKT values (determined for each room individually) for the same room type, considering sample number for each population.

City	Bedroom		Bathroom		Living room		Kitchen		Limited use rooms		Car	
	TEMP (°C)	%RH	TEMP (°C)	%RH	TEMP (°C)	%RH	TEMP (°C)	%RH	TEMP (°C)	%RH	TEMP (°C)	%RH
Jeddah	17.5–30.7	36.9–64.4	24.6–31.6	33.0–88.0	23.2–33.4	22.3–73.1	25.4–31.0	35.7–51.8	25.1–34.2	36.1–75.0	26.8–71.0	9.2–72.4
Medina	16.7–30.7	36.9–64.4	25.5–35.5	13.7–79.9	27.0–32.9	18.0–28.6	25.9–33.0	17.1–31.6	28.9–34.2	16.6–31.3	27.7–68.9	6.6–35.7
Khobar	23.6–34.5	20.8–49.9	30–31.6	28.6–66	27.6–31.7	31.7–41.9	27.6–31.7	31.7–41.9	28.9–30.8	31.3–23.8	–	–
Pooled Average	24.5 ± 2.3	47.4 ± 4.3	30.4 ± 0.5	39.1 ± 6.7	29.5 ± 1.5	37.9 ± 3.7	29.7 ± 1.5	34.6 ± 9.1	31.7 ± 0.9	37.6 ± 3.0	54.2 ± 0.5	20.4 ± 8.4

less, further validation of temperature and %RH measurements (in the range 10–70 °C, 10–90 %RH) were performed using calibrated instruments. Readings from data loggers were equal to those determined using calibrated instruments with a ±0.5 °C variation for temperature measurements and ±5% for %RH.

3.3.2. Temperature and relative humidity mapping

Room temperature (RT) and relative humidity (%RH) was monitored over 24 h (during the months of June and July 2020) in 5 room types: Bedrooms, Bathrooms, Living rooms, Kitchens and Limited use rooms (e.g. guest rooms). Results from preliminary experiments of monitoring a room's temperature and %RH for 3 consecutive days, with no change in its daily usage routine, have shown no significant difference in its daily MKT. At least 6 rooms were sampled for each room type. Samples were from 7 different houses across three cities (Jeddah, Medina and Khobar) in Saudi Arabia. Jeddah and Khobar were selected due to their high temperature and relative humidity (Howarth et al., 2020), while Medina was selected for its high temperature and low humidity (Khan and Alghafari, 2016). This was further confirmed in communications with The General Authority of Meteorology & Environmental Protection in Saudi Arabia, otherwise referred to as Presidency of Meteorology and Environment (PME, 2020).

Collected data was analysed to determine the MKT for each room over a 24-hour period (Fig. 4). In addition, the range observed in RT and %RH for each room type, categorised by city, was determined (Table 3). Using two-way ANOVA analysis, MKT and %RH of different room types were determined significantly different ($p < 0.05$).

Temperature and %RH of car interior (parked and exposed to sunlight) were also monitored over a 24-hour period, by placing data loggers on driver adjacent seats. Recorded temperature readings in Jeddah exceeded 70 °C for more than two hours (Table 3). Similar temperatures were recorded when repeating the experiment in Medina (Table 3).

4. Discussion

In compliance with regulatory bodies around the world, pharmaceutical companies go to great lengths in ensuring pharmaceu-

tical products maintain their specifications, essential for their performance as medicinal dosage forms, throughout their shelf-life (ICH, 1996a,b, 2002, 2003a,b). This is determined through long-term stability studies at temperature and humidity ranges specified in various ICH guidelines (ICH, 1996a,b, 2003a,b). After which, a shelf-life at appropriate storage conditions is determined for each product (ICH, 2003a,b). Furthermore, to ensure product quality after leaving pharmaceutical manufacturing facilities, product packaging is labelled with clear storage instructions. Most important of which addresses critical storage temperature ranges, based on previously performed stability studies (ICH, 2003a,b). Regulatory bodies, such as the Saudi Food and Drug Authority (SFDA), also enforce strict regulations on companies involved with transportation, storage and sales, to ensure storage conditions are monitored and maintained within manufacturer specified limits; up until those products are dispensed to patients.

Very little is known about the conditions in which households in Saudi Arabia maintain and store their medicinal products. Although in some cases, medication maybe administered shortly after being dispensed, however in this study, long term-storage (>30 days) of medications was shown to be a common practice among households in Saudi Arabia. The most common reasons for storing medication at home include first aid. The majority of participants have claimed to regularly store OTC medicines used in treating symptoms of common conditions, such as the common cold and common gastrointestinal conditions. Households with chronic illnesses on the other hand generally receive a supply of medication at a time. Using long duration repeat prescriptions, such patients may hold as much as a four month supply of medication (King et al., 2018). The use of food supplements was another reason households store pharmaceutical products at home. While such products are not treated with POM restrictions, they do contain APIs that can degrade when stored incorrectly (Garrett, 1956).

A great proportion of households in Saudi Arabia have shown compliance with good storage practices for pharmaceutical products. These include reading vital storage instructions on product packaging, checking the expiration date before use and storing medicines in their original packaging. Similar findings were published by Koshok et al. (2017), however, data generated from questionnaires and surveys may suffer from response bias. This may include social desirability bias (Paulhus, 1991; Grimm, 2010; Bogner and Landrock, 2016), where participants attempt to project a better and more responsible image of themselves by claiming to comply with good storage practices. As a result, the true percentage of households who partake in good storage practices maybe lower than perceived. This is further confirmed when participants' knowledge was tested, while the majority were aware of the harmful effect heat and humidity may have on medicines, fewer participants selected exposure to air and light as factors one should consider. Not only could light cause direct photodegradation to some APIs, but when pharmaceutical products are directly exposed to sunlight, their temperatures may increase significantly, while the RT is maintained within limits (Heinemann et al., 2020). Results from this study have also revealed inappropriate storage practices such as storing liquid medications in freezers. This can cause changes in the physical state of solutes, leading to its precipitation and therefore the lowering of drug concentration and dose administered (Kolhe and Badkar, 2011). In a separate question, just over half of participants have selected appropriate storage conditions as dark and dry, while the remaining participants have either opted to not knowing the most appropriate conditions or have selected inappropriate conditions. These results may indicate a lack of awareness for households in Saudi Arabia, also noted by several recent publications (Al Ruwaili et al., 2014; Koshok et al., 2017; Altebainawi et al., 2020).

In addition to lack of awareness on appropriate storage practices, households in Saudi Arabia may be limited to storage environments susceptible to the warm climate observed in many regions, especially during the summer (Howarth et al., 2020). In this study, RTs of various room types were monitored in a number of different homes and regions within Saudi Arabia. While many factors play a role in influencing such temperature, including thermal insulation in buildings, performance and availability of air conditioning and room size (Howarth et al., 2020), results from this study have shown all room types to reach or exceed MKT of 25 °C. This may be due to the infrequent/absent use of air conditioners. Bathrooms in particular are not equipped with air conditioning in most homes in Saudi Arabia, and despite of the common practice observed in global media, where medicines are shown to be stored in bathroom cabinets, results from this study suggest this to be very inappropriate in Saudi Arabia. Furthermore, participants claiming to store medications in bathrooms were found to rate the performance of their medications the lowest ($p < 0.05$). While storing medication in a bedroom may be safer as MKTs are on average the lowest of all room types. Medications stored in bedrooms are still, in some homes, exposed to MKTs above those specified by manufacturers.

Due to difficulties accompanied with finding volunteer households welling to take part in temperature and % RH mapping of their homes, this study was limited to 7 non-randomly selected homes. This as a sample size is not sufficient to represent the population of homes in the region, nevertheless it can give an indication as to which room types households should avoid storing medication in, based on their usage and the availability of air conditioning. Results from this study have also shown MKT of car interiors (over a 24-hour period) to exceed 50 °C, thus very likely causing irreversible harm to medicinal products stored in cars (Hii et al., 2019). While data from questionnaire showed majority of participants claiming not to store medicines in their cars, this may be influenced by social desirability bias.

Storing thermally sensitive medications in a temperature-controlled fridge could be the only way, for households in Saudi Arabia, to ensure medications are maintained within storage conditions specified by manufacturers. Though, storing medications with food products in a commonly used family fridge is considered unsafe for children in the house (Wiseman et al., 1987).

Fig. 5. Illustrating an example of how Time-Temperature Indicators may be utilised as a solution to warn consumers when medication has been exposed to conditions outside those specified by the manufacturer. The horizontal bar undergoes a change in color from white to red (starting from the left side) when RT is greater than a specified limit. The rate of change can be made proportional to RT, where no change takes place if RT is below a specified limit. When the bar undergoes complete change, thus red marker has reached the right side, consumers are advised not to use the product despite remaining shelf-life.

Investing in a small secure fridge dedicated for storing medicinal products might be the safest option for households in Saudi Arabia.

Smart packaging solutions is an added precaution that can help households monitor the quality of their stored pharmaceutical products (Yousefi et al., 2019). TTIs in the form of labels (affixed to product packaging) can offer households with accumulated thermal history, medicinal product were exposed to, and hence the remaining shelf-life, based on drug quality kinetics (Wang et al., 2015). Such smart packaging solutions have been extensively researched and utilised in the food industry. Numerous patents were published throughout the past years, overcoming many challenges in the implementation of TTI use, such as high financial cost (Wang et al., 2015; Choi et al., 2020; Gao et al., 2020; Hui et al., 2020). The use of TTIs in the pharmaceutical industry is still shy, Oxytocin is one of the few products where TTIs were utilised due to its high thermal sensitivity (Stanton et al., 2012).

The observed high room temperatures in this study can justify the use of TTIs on more pharmaceutical products in Saudi Arabia, especially when storage instructions include temperatures below 25 °C. Furthermore, the use of TTIs on thermally sensitive pharmaceutical products in Saudi Arabia can enhance quality assurance of products throughout distribution, storage and beyond dispensing. A visual indicator of the thermal history of a sensitive pharmaceutical product can greatly enhance consumer awareness of the importance of maintaining such product within specified storage conditions. Furthermore, it can help prevent dispensing pharmaceutical products with undesirable thermal history. Fig. 5 illustrates an example of how TTIs may be utilised in pharmaceutical products and thus help consumers make an appropriate decision on storage conditions and usage of long stored products.

5. Conclusions

Very little was published on how medications are treated after being dispensed. Although clear storage instructions are printed on medication packaging, compliance is subject to availability of suitable storage conditions. This study has shown that all rooms in a typical home in Saudi Arabia can exceed storage temperatures commonly specified by pharmaceutical manufacturers, thus exposing such products to possible thermal degradation and the shortening of shelf-life. Awareness of good storage practices and the factors that can influence the stability of medicinal products is key in enhancing quality assurance after product dispensing. Many participants have shown a knowledge gap when it comes to these factors.

To ensure products are maintained within manufacturer recommended storage conditions, the author encourages households to invest in a secure small fridge with temperature controls. The utilisation of Time-Temperature Indicators for thermally sensitive products in Saudi Arabia is very justified and can have a significant impact on quality assurance pre and post dispensing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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